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UK Guidelines on ^{18}F-Fluciclovine PET/CT in Prostate Cancer Imaging 1.0

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Purpose

The purpose of these guidelines is to assist specialists in Nuclear Medicine and Radionuclide Radiology in recommending, performing, interpreting and reporting ^{18}F-fluciclovine PET/CT. It should be recognised that adherence to the guidance in this document will not assure an accurate diagnosis or a successful outcome. These guidelines will assist individual departments in the formulation of their own local protocols. The guidelines apply to studies on adults. All that should be expected is that the practitioner will follow a reasonable course of action based on current knowledge, available resources and the needs of the patient in order to deliver effective and safe medical care.

Background

^{18}F-Fluciclovine PET/CT is a non-invasive imaging technique which relies on the evaluation of amino acid metabolism in the setting of upregulated amino acid transport systems in prostate cancer. ^{18}F-Fluciclovine is a synthetic amino acid which is transported by sodium-dependent channels [specifically system ASC (ASCT2) with a contribution from sodium-independent system L (LAT1)] [1].

Goals

This document aims to provide guidance to nuclear medicine physicians and radiologists on the indications for and the methods of performing and reporting ^{18}F-fluciclovine PET/CT imaging in the setting of biochemical recurrence of prostate cancer, and to standardise quality control and assurance procedures. The guidelines are based on the best available evidence or, where this is lacking, on the clinical experience of the authors in consensus. They are intended to help departments produce studies of the highest quality and clinical utility. Areas for future research are also discussed.

Definitions

PET/CT scanner:

An imaging instrument which allows molecular information (PET) and anatomical detail (CT) to be acquired sequentially as part of a single study. The two data sets can be fused

accurately provided there is no significant patient movement during the imaging acquisitions.

Biochemical recurrence:

A rise in serum prostate-specific antigen (PSA) in a patient post radical treatment with curative intent, either surgery (prostatectomy) or radiotherapy. Also called biochemical relapse and PSA failure, the precise threshold of PSA rise required to determine disease relapse is dependent upon the initial curative treatment.

Restaging:

A process used to determine the amount or spread of cancer in the body in the event of recurrence or progression after treatment with the intention of informing the choice of treatment.

Castrate-resistant metastatic prostate cancer (CRPC):

Metastatic prostate cancer that has progressed following either medical or surgical castration.

Indications

^{18}F-Fluciclovine PET/CT imaging is indicated in patients with suspicion of recurrent prostate cancer based on elevation of the PSA level following prior treatment with curative intent and is performed with the intention of guiding or optimising salvage treatment.

The criteria outlined in this article are based on the currently available evidence, including data from prospective clinical trials as well as the authors' experience of using this tracer.

<u>Localisation of tumour in recurrent prostate cancer</u>

Published data exist on the use of ^{18}F-fluciclovine for localisation of prostate cancer in the setting of biochemical recurrence [2–9]. The aim of assessment or restaging in this setting is to potentially guide salvage therapy. Clinically acceptable diagnostic performance was demonstrated in the international multicentre setting, where subject level detection rate at

a low PSA (≤0.79 ng/ml) was 41%, with a positive predictive value of 92% for detection of extra-prostatic disease [10]. Two major multicentre clinical trials have recently evaluated the impact of ^{18}F-fluciclovine on the management of patients with biochemical recurrence. In the United States-based LOCATE trial [2], ^{18}F-fluciclovine PET/CT led to a major change in management in 59% (126/213) of patients with negative or equivocal conventional imaging (CT/bone scan/MRI). These results are concordant with those of a similar UK study (FALCON), which demonstrated that 61% (52/85) of patients had a major change in management after an ^{18}F-fluciclovine PET/CT scan, meeting a pre-specified condition defining overwhelming efficacy [11].

Greater diagnostic accuracy in comparison with ^{11}C-choline PET/CT has been reported by Nanni et al. in 89 patients who underwent investigation with both tracers [6]. ^{18}F-Fluciclovine PET/CT allowed more accurate restaging in patients with biochemical recurrence; furthermore, its sensitivity was 37% compared with 32% for ^{11}C-choline and its specificity was 67% compared with 40% for ^{11}C-choline. Greater detection of disease sites was particularly evident at low PSA levels (21% and 14% for ^{18}F-fluciclovine and ^{11}C-choline respectively at a PSA level of <1 ng/ml, and 45% and 29% respectively when PSA was between 1 and <2 ng/ml).

Emerging applications

The licenced indication for ^{18}F-fluciclovine is limited to detecting recurrence of prostate cancer in adult men with biochemical recurrence of prostate cancer. Nonetheless, there are specific areas where conventional imaging may benefit from supplementation with PET/CT in prostate cancer. In the primary setting, typically in patients with high-risk disease, equivocal conventional findings (for example a borderline abnormal lymph node on CT or MRI or equivocal uptake on a bone scan) could potentially be resolved with ^{18}F-fluciclovine. This is already recommended by the joint RCR-RCP guidelines for ^{18}F-choline PET/CT and ^{68}Ga-PSMA PET/CT [12].

In the evaluation of the primary tumour, ^{18}F-fluciclovine PET/CT may potentially aid the localisation of intra-prostatic tumour and guide targeted biopsy in cases in which MRI is contraindicated or severely limited (e.g. by non-resolvable artefact), with ongoing studies evaluating this potential indication.

In advanced metastatic disease, response evaluation currently relies on CT and bone scans, which may fail to detect progression at early intervals. Research on ^{18}F-fluciclovine PET/CT in this setting may allow earlier treatment modification in CRPC.

Contraindications

Hypersensitivity, to the active substance or excipients, when used in men being investigated for biochemical recurrence of prostate cancer.

Regulatory requirements

Administration of Radioactive Substances Advisory Committee (ARSAC) licences for fluciclovine will normally be held by radionuclide radiology/nuclear medicine specialists. The prospective licence holder needs to provide proof, when applying for an ARSAC licence, that they have undergone appropriate theoretical and supervised practical training. Training materials that are suitable for submission as evidence for a practitioner license are available direct from Blue Earth Diagnostics Ltd. Under the new IRMER guidelines, the site licence will have to show that ^{18}F PET tracers can be used at the site [13].

^{18}F-Fluciclovine (Axumin^{TM}) was approved by the US Food and Drug Administration in May 2016 and by the European Medicines Agency in May 2017 [14, 15] for PET imaging in biochemical recurrence of prostate cancer. National Comprehensive Cancer Network guidelines published in 2018 state that fluciclovine PET/CT can be considered for recurrence or disease progression after definitive therapy or for disease progression during systemic therapy (National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer Version 2.2018. June 3, 2018. Available online: https://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf). The 2019 European Association of Urology (EAU) guidelines on prostate cancer management also advocate the

use of ^{18}F-fluciclovine PET/CT in patients with PSA recurrence who are fit for curative salvage treatment (https://uroweb.org/guideline/prostate-cancer/).

Qualifications and responsibilities of personnel

See European Association of Nuclear Medicine procedure guidelines for tumour PET imaging, version 2.0 or the Society of Nuclear Medicine and Molecular Imaging Procedure Standard for General Imaging [16, 17].

Procedure/specification of the examination

Necessary data for requesting examination

In order for correct justification/vetting to be performed by a medical practitioner, as well as to improve the quality of the report of the study, key elements of the patient's history should be declared on the imaging request. These include:

- Specific question being asked (e.g. Where is the location of tumour recurrence?)
- Diagnosis
- Risk group (based on PSA, T stage and Gleason score)
- Treatment history (e.g. radiotherapy or prostatectomy)
- Current PSA values
- Serial PSA values and PSA kinetics (velocity and doubling time)
- Relevant findings from other investigations (e.g. MRI)
- Current medications and allergies
- Symptoms (e.g. bone pain)
- Relevant co-morbidities (e.g. co-existing malignancy)

Patient preparation

Patients should avoid strenuous activity for 24 h prior to ^{18}F-fluciclovine injection. Fasting is required for at least 4 h prior to the study with only small sips of water and any regular medications permissible. To reduce the potential impact of early urinary excretion (in a minority of patients) into the bladder, patients should be encouraged to void approximately

30-60 minutes before scanning. Prior to injection, a focussed history should be taken, including confirmation of the reason for the study, treatment history, list of medications, allergies and any co-morbidities, including any clinical changes since last seeing the referring clinician, such as infection or trauma. Confirmation of fasting status and lack of strenuous activity for 24 h should be documented at this stage.

Radiopharmaceutical injected activity

The suggested target injected activity of ^{18}F-fluciclovine is 370 MBq. An activity >20% below this target may result in suboptimal image quality. The recommended maximum volume of injection of undiluted ^{18}F-fluciclovine is 5ml. The dose may be diluted with 0.9% sodium chloride for injection by a factor of 8. It should be noted that other factors such as patient size, scanning mode (2D or 3D) and proportion of bed position overlap will impact on the administered activity.

Radiation exposure to the patient

An administered activity of 370 MBq will result in an effective dose of 8.2 mSv. A maximum effective dose of 7 mSv would be expected due to the CT scan, depending on the scanner.

Imaging procedure

The study should be performed by two technologists or other qualified personnel. The administration should be carried out with the patient on the scanning couch.

Injection in the right arm is preferred as stasis in the axillary vein on the left may be misinterpreted as a metastatic lymph node (Virchow's node).

After the injection has been completed, the patient should be asked to raise his arms above the head in preparation for the scan acquisition (to avoid beam-hardening artefacts). If the patients cannot tolerate this position for the duration of the study, a different patient positioning may be chosen.

CT settings

The CT performed as part of the PET/CT protocol provides attenuation correction information and diagnostic information that is relevant to overall patient care.

A number of CT protocols exist for PET/CT scanning. However, in general a low-dose CT acquisition for anatomical correlation and attenuation correction is recommended with ^{18}F-fluciclovine. In a patient with a hip prosthesis, it is advisable to modify the protocol to reduce the artefact [18].

A CT scout view is acquired for selection of the PET/CT axial field of view. A low-dose CT scan will be acquired for attenuation correction and anatomical correlation. It is recommended that respiration is not suspended during CT imaging, and the patient should be coached in shallow/quiet breathing. Gating of the PET and/or CT may benefit the breathing pattern. The use of intravenous or oral contrast is not required, however if intravenous contrast is standard of practice at a site it is recommended that this take place after the ^{18}F-fluciclovine PET/CT scan.

PET settings

PET scanning should begin 3–5 min after completion of the injection administration (target 4 min). Image acquisition should start from the proximal thigh and proceed to the base of the skull. The first bed position should be centered on the prostate bed (indicated by the pubic symphysis) and include the femoral heads and inguinal nodes.

Typical total scan time is between 20 and 30 min. The duration of acquisition over the pelvis (i.e. pubic symphysis to iliac crest) can be increased in order to improve the sensitivity of detection of disease in common sites of lymph node metastasis (e.g. GE Healthcare PET/CT using default bed overlap: acquire for 5 min for the first two bed positions over the pelvis and for 3 min per bed position for the remaining bed positions).

The local radioactivity concentration can be measured on attenuation-corrected images which have been normalised for injected activity and body weight, lean body mass or body

surface area. This can be recorded as the standardised uptake value (SUV). Multiple factors, including accuracy of calibration of the PET device, will influence the accuracy of the SUV.

After completion of the scan, the patient should be removed from the scanner and encouraged to void before leaving the PET facility. The patient should be encouraged to drink plenty of fluids and void frequently throughout the day.

Local procedures for the management of patients undergoing ^{18}F PET procedures should be followed (e.g. restricted contact with infants and pregnant women for 4 h post injection, provision of patient post-care and radiation information sheets).

A sample standard operating protocol is presented in Appendix 1.

Image reconstruction

Reconstruction algorithms should be based on the manufacturer's recommendations. Reconstruction modifications can best be achieved using the manufacturer's guidelines in conjunction with the institution's physician and physicist recommendations. Resolution recovery may help with the detection of small lesions, however the size criteria for image interpretation may change. For example, a 1 cm lesion without resolution recovery may be equivalent to a sub-centimetre lesion with resolution recovery.

The reconstructed PET data should be corrected for decay, dead time, scatter, randoms and attenuation using standard algorithms provided by the scanner manufacturer. Attenuation correction should be performed using the low-dose CT. Iterative reconstruction should be used, e.g. OSEM or similar. Time of flight (ToF) reconstruction should be used when available.

Documentation and reporting

The use of standardised interpretation methodology for the assessment of ^{18}F-fluciclovine PET/CT images has also been shown to enable naïve readers to achieve acceptable diagnostic performance and reproducibility when staging recurrent prostate cancer [19].

The PET/CT image review format will depend on the local workstation and software packages available. However, key data sets will include CT alone, ^{18}F-fluciclovine PET (attenuation corrected and non-attenuation corrected) and fused PET/CT, and these should be reviewed in axial, coronal and sagittal planes as well as the maximal intensity projection (MIP) view of the PET images.

As described above, ^{18}F-fluciclovine has particular benefit over ^{18}F-choline in detecting disease recurrence at lower PSA levels. However, no threshold is recommended beyond which ^{18}F-fluciclovine should be performed. Positive ^{18}F-fluciclovine uptake is more likely at PSA >1 ng/ml with rapidly rising PSA kinetics (e.g. dt < 6 months) before the PSA level of 1 ng/ml is reached.

Evaluation of abnormal uptake of ^{18}F-fluciclovine will require a detailed knowledge of physiological tracer uptake, false positives and the pathways of disease dissemination in prostate cancer [20]. Typical physiological sites of uptake are presented in Table 1.

If a site of uptake is deemed pathological, the SUV measurement can be obtained and compared with non-target tissue background activity **(Figures 1, 2)**. Focal lesions suspicious for disease will usually have uptake greater than bone marrow (L3 vertebral body is preferred). Small lesions (<1 cm) may still be considered metastatic if the avidity is similar to marrow uptake but greater than blood pool uptake. This approach holds true for disease in the prostate, seminal vesicles, prostate bed and lymph nodes [21]. Bone metastases are usually identified by focal uptake on the MIP image, with uptake typically higher in lytic than in sclerotic or mixed sclerotic lesions. Densely sclerotic lesions may be non-avid.

Pitfalls in interpretation

False positive sites of ^{18}F-fluciclovine uptake include infection, inflammation in the prostate (including post radiation) and benign prostatic hypertrophy [20]. Lymph nodes may be ^{18}F-fluciclovine avid in the presence of infection, inflammation and other (non-prostate) malignancies including colon cancer, lymphoma and breast cancer. Benign bone lesions which may be ^{18}F-fluciclovine avid include osteoid osteoma and degenerative changes. Malignant bone lesions from non-prostate malignancies may also be tracer avid, including

multiple myeloma. Reactive lymph nodes may display tracer uptake and consideration should be given to potential underlying causes for this, e.g. vascular grafts. Variable uptake is recognised in musculoskeletal and cutaneous inflammation [20].

False negative studies may occur at very low PSA levels and in the presence of densely sclerotic bone lesions. In a minority of patients, early bladder activity may impede disease detection in the prostate bed. These pitfalls are presented in Table 2.

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Table 1: **Degree of uptake at physiological sites.**

Mild	**Moderate**	**Intense**	**Heterogeneous**
Salivary glands and lymphoid tissue of Waldeyer's ring	Pituitary gland	Liver	Bone marrow
Thyroid gland		Pancreas	Cardiac and skeletal muscle
Breast parenchyma			
Oesophagus and stomach			
Renal parenchyma			
Periurethral activity			
Urinary bladder wall			
Adrenal glands (can be intense)			
Small and large bowel			

Table 2: **Pitfalls in image interpretation.**

False positive causes	False negative causes
Prostate/ prostate bed	
BPH Post-treatment (radiotherapy)/ inflammation Infection	Small-volume disease Early bladder activity obscuring disease Low-grade/indolent tumour
Lymph node	
Reactive nodes, e.g. adjacent to vascular graft Other malignancy	Small-volume/ micrometastatic involvement Low-grade/indolent tumour
Bone	
Degenerative change Osteoid osteoma Other malignancy	Densely sclerotic metastases Small-volume/ micrometastatic involvement Low-grade/indolent tumour
Other	
Musculoskeletal and cutaneous inflammation Other malignancy	

Figure 1: 62 year old, Previous radical prostatectomy for pT2B N0 M0, Gleason 8 disease Biochemical recurrence – PSA 0.6 µg/L, PSA_{dt} 8.8 months, Intended management, Salvage radiotherapy to the prostatectomy bed.

^{18}F-fluciclovine scan confirmed an avid focus within the prostatectomy bed at the vesicourethral anastomosis. This was aided by the presence of only minimal radioactivity in the urinary bladder. Patient received RT limited to the prostatectomy bed.

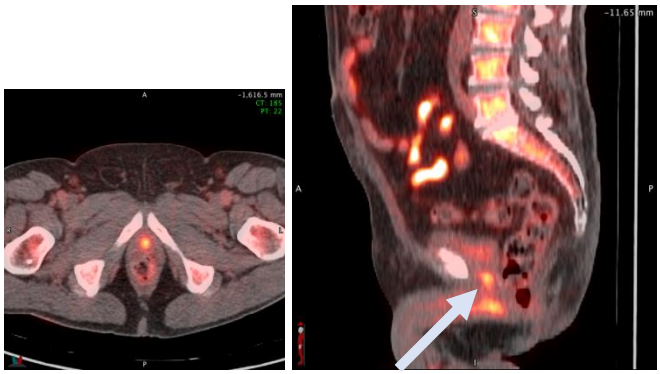
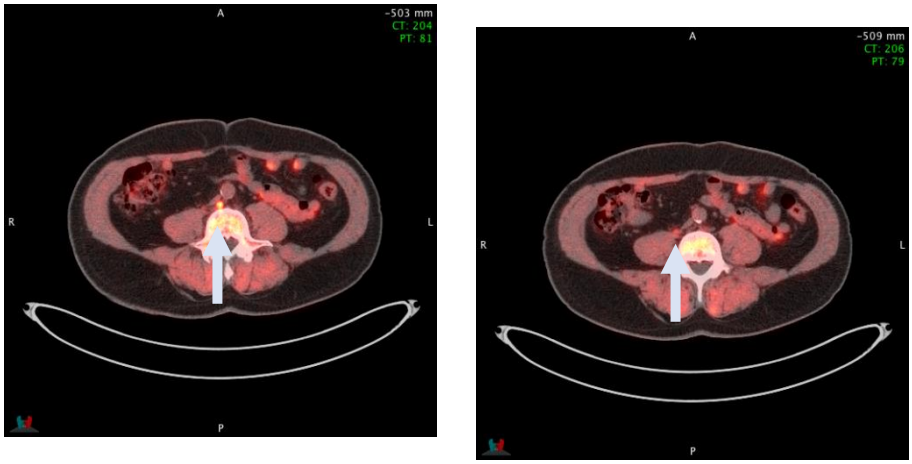


Figure 2: 71 year old man, previous radical prostatectomy for T3A N0 M0, Gleason 9 disease, Biochemical recurrence – PSA 0.73 µg/L. Intended management androgen deprivation therapy.

With positive delineation of these ^{18}F-fluciclovine avid retroperitoneal nodes, the management plan was revised to include targeted salvage treatment of this area.



Appendix 1.

Sample SOP for ^{18}F-fluciclovine PET/CT.

SOP:		TITLE:	^{18}F-Fluciclovine PET/CT in patients with prostate cancer with biochemical recurrence after radical treatment		
Rev:		Date:		Review date	
Group:		Author:		Authorised:	

OVERVIEW AND SUMMARY

^{18}F-Fluciclovine PET/CT in patients with prostate cancer with biochemical recurrence after radical treatment.

The purpose of this investigation is to identify any tracer-avid disease from prostate cancer. Local disease, lymph nodes and bone disease are amongst the commonest sites of disease spread. Patients undergoing this investigation will have recurrence of disease, i.e. have had previous (radical) treatment.

Important Notes:

- ^{18}F-Fluciclovine administration is to be performed on the PET/CT scanner bed.
- Imaging begins 3–5 min after tracer injection (target 4 min), starting from the proximal thigh and proceeding towards the head
- The target administered activity is 370 MBq ±20%. Minimum amount: 296 MBq; maximum amount 444 MBq.
- Stop watch to be used to ensure appropriate recording of injection times and scan start times.
- Scan coverage : proximal thigh to skull base

REQUEST

Valid reasons for examination:

- Indications: Patients with prostate cancer with biochemical recurrence who are being considered for radical salvage treatment (with curative intent), having had primary radical curative therapy

JUSTIFICATION AND AUTHORISATION

Valid referrers:
Clinical consultants and members of the uro-oncology MDT

Persons who may vet:
ARSAC licence holder or delegate

Justification code:
Locally agreed

Booking

- Patient asked to fast for 4 h (only sips of water allowed). Patients may take medication as normal prior to the scan (even if this does not take place, proceed with scan as planned).
- Patient asked to avoid significant exercise during the 24 h before the scan (even if such exercise does take place, proceed with scan as planned).
- Dose ordering by local protocol.
- Scan booking slot is 30 min only. For booking purposes, the injection time should be scheduled 30 min prior to the scan time.
- Patients should be asked to arrive at least 30 min before the injection time.

PATIENT PREPARATION

- Ask patient to change into a gown and check for metal objects.
- Measure height and weight (do not rely on the patient's self-reported measures).
- Encourage patient to void bladder immediately prior to starting the scan.
- Ensure stopwatch is available to guarantee accurate time recording.
- No intravenous contrast media should be administered during the PET/CT study.

RADIOPHARMACEUTICAL AND ADMINISTRATION	
Radiopharmaceutical:	^{18}F-fluciclovine
ARSAC Serial No:	Certificate No.
DRL: (Maximum usual activity)	444 MBq
ED:	8.2 mSv
Minimum dose for paediatrics:	N/A
Advice re breastfeeding:	N/A
Persons who may administer:	Departmental list
Route of administration: (IV etc)	IV
Advice after administration:	Void bladder immediately after scan and frequently for the rest of the day. Keep well hydrated.

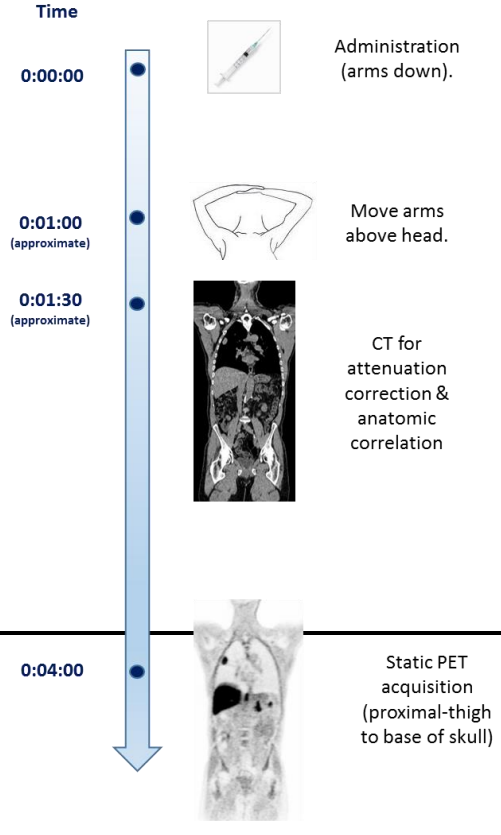
ACQUISITION PARAMETERS

Landmark	Sternal notch		
CT Acquisition Protocol	PROSTATE CA 18F-FLUCICLOVINE		
CT Acquisition Parameters	Scout 120 kVp, 10 mA CT 120 kVp, 80 mA , 0.8 s, helical pitch 1.375 CT AC 3.75 mm thick (70-cm FoV Q.AC Wideview 400/40), WB Standard 2.5 mm (50-cm FoV, Stnd 400/40), CT Lung 2.5 mm (50-cm FoV Lung 400/40)		
PET Acquisition Protocol	Eyes to Thighs Emission		
PET Acquisition Parameters	3D, 5 min for first two inferior bed positions, 3 min thereafter; scan direction towards head; matrix size 256×256		
PET Reconstruction Protocols	TOF	TOF PSF	NAC
PET Reconstruction Parameters	MAC 24 subs, 2 iterations VPFX 6.4 mm FWHM Slice thickness 3.27 mm Recon. diameter 70 cm	MAC 18 subs, 3 iterations VPFX-S 4.0 mm FWHM Slice thickness 3.27 mm Recon. diameter 70 cm	NAC 24 subs, 2 iterations VPHD 6.4mm FWHM Slice thickness 3.27 mm Recon. diameter 70 cm

INJECTION + ACQUISITION TECHNIQUE

- Ensure CT tube warm-up complete before admitting patient into scanning room

Overview:



- Cannulation: ideally done prior to patient being placed onto scanner bed.

- Right arm vein cannula preferred; ensure patency prior to starting the scanner procedure.

Dose Preparation:

- The target administered activity is 370 MBq ± 20%.

- The minimum administered activity is 296 MBq and if the amount of activity available is less than this amount, the patient will be re-scheduled to be scanned on another occasion.

- The maximum amount of activity to be administered is 444 MBq.

- The maximum volume of ^{18}F-fluciclovine injection to be administered is 5 ml (i.e. 5 ml of undiluted radiopharmaceutical). The administered dose can be diluted up to 10 ml with 0.9% saline (as required).

Ensure CT tube warm-up complete before admitting patient into scanning room

Scanning:

Time to injection: **10 min before start**

- Position the patient in the PET/CT using the lasers and set the landmark using internal/external landmark

- Injection site monitoring (make note of any abnormalities, e.g. redness, pain or swelling on injection site)

Time of injection: **0 min**

- Position patient's arms alongside torso

- Administer ^{18}F-fluciclovine injection as a slow intravenous injection into the right arm over 1 min. An example of an appropriate administration routine (for a 10 ml injection) would be to inject 1 ml ^{18}F-fluciclovine, wait 5 s, inject 1 ml ^{18}F-fluciclovine, wait 5 s etc.

- Flush with ≥10 ml saline

- The time of the end of the administration should be recorded

- Injection site monitoring (make note of any abnormalities, e.g. redness, pain or swelling at injection site)

- Assessment of post-administration events

- Position the patient's arms above their head
- The residual activity in the tubing or syringe, or that was spilled during injection, should be recorded

Time post injection: **1.5–2 min post injection**

- Ensure any doors from the PET/CT room are locked to avoid non-study personnel entering room
- Inform patient about noise from CT tube and bed movement
- Acquire a CT scout view for selection of the PET FOV
- Acquire a CT for attenuation correction and anatomical correlation from proximal thigh to skull base
- NB: **CTAC must not be repeated due to CT dose limit constraints**

Time post-injection: **3–5 min post injection**

- PET scanning should begin from 3 to 5 min after completion of the injection administration (target 4 min). N.B. **Ensure scan starts from proximal thigh**

Time post injection: **20–30 min post injection**

- Approximate end of emission scan – remove patient from PET/CT scanner
- Take the venous cannula out, applying standard precautions

Complete PET/CT acquisition form

ADVICE TO PATIENT ON DISCHARGE

Encourage patient to void bladder on removal from the scanner. Encourage patient to drink plenty of fluids and to void bladder frequently throughout the day. Patient may eat and drink as normal.
Local procedures for the management of patients undergoing ^{18}F PET procedures should be followed (restricted contact with infants and pregnant women for 4 h post injection, provision of patient post care and radiation information sheets)

DATA ANALYSIS

None of note

DATA DISPLAY

Fused axials and MIP

REPORTING

Persons who may report:

Trained Nuclear Medicine consultants.

Reporting Procedure:

- Clinical indication
- Technique/acquisition details
- Findings:
- Sites of disease (particular reference to prostate/prostate bed, seminal vesicles, lymph nodes, bone, liver and lung)
- Any other sites with a non-physiological pattern of tracer uptake
- Any important findings from CT component (particular care should be taken to identify densely sclerotic, non-avid lesions)
- Conclusion

DATA ARCHIVING

Send all image series acquired to PACS except for Raw Emission Data set.

- WB standard
- CT lung
- WB TOF
- PET NAC
- Dose report

Any local agreed archiving

REVISION HISTORY

Rev No	Date	Author	Changes	Reviewed by